enhance our ability to diagnose and treat malignant tumors.

CONFLICT OF INTEREST
James M. Grichnik is major shareholder and founder of DigitalDerm Inc. (MoleMapCD) and Malachite Corporation (medical databases).

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See related article on page 1281, 1286, and 1292

More than One Gene Involved in Monilethrix: Intracellular but also Extracellular Players

Jürgen Schweizer[1]

Monilethrix, an autosomal dominant human hair disorder, is caused by mutations in three type II hair cortex keratins. Rare cases of the disease with non-vertical transmission have now been found to overlap with localized autosomal recessive hypotrichosis. The underlying gene, desmoglein 4 (*DSG4*), belongs to the desmosomal cadherin superfamily and is also expressed in the cortex of the hair follicle.

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In 1997 it was demonstrated that the principle of a causal relationship between mutated epithelial keratins and human genodermatoses holds true also for mutated hair keratins and hereditary hair disorders. The respective disease, monilethrix (from the Latin for "necklace" and the Greek for "hair"; OMIM #158000 and #252200), is considered an autosomal dominant condition with high penetrance but variable expression and belongs to a variety of congenital hair diseases whose hallmark is an unusually deformed hair shaft. Monilethrix was so named for the beaded appearance of affected hairs. These exhibit elliptical nodes of normal thickness that are regularly separated by dystrophic constrictions. The internodes possess a high propensity to break, leading to alopecia; that is, short stubble hair associated with follicular keratosis and perifollicular erythema. In the mildest form, the disease involves only the occiput and the nape of the neck, but in its severe form, the entire scalp, secondary hairs, eyebrows, and eyelashes may also be involved. In addition, subtle nail defects have been reported. Occasionally, regrowth of apparently normal hair may occur at the time of puberty or during pregnancy. Ultrastructurally, vacuolation and alterations in the fibrillar structures of lower cortex cells have been described (for a review, see Langbein and Schweizer, 2005).

The three hair keratin genes that proved to be causal for monilethrix encode the type II hair keratins Hb1, Hb3, and Hb6, which share a completely identical α-helical rod domain and, in line with the ultrastructurally observed disease symptoms, are all expressed in the hair cortex. Besides sporadic mutations in the 1A helix initiation motif, two non-conservative mutational hot spots in the 2B helix termination motif, Glu413Lys and Glu402Lys, were observed, Glu413Lys being most frequent in Hb6 and Glu402Lys being more abundant in Hb1 (Langbein and Schweizer, 2005). Curiously enough, up to now, only one monilethrix family exhibiting the equivalent of the Glu402Lys mutation in Hb3 (Glu407Lys) has been reported (van Steensel *et al.*, 2005). The numerous monilethrix families that have been investigated since 1997 indicate that there is no genotype–phenotype correlation for the disease. One impressive example of the variability of the phenotype was noted in a pedigree in which, of three carriers of the Hb1 Glu402Lys mutation, two children exhibited beaded hairs that were visible either to the naked eye or upon electron microscopic inspection. In contrast, their mothers' hairs appeared completely healthy, but the moniliform phenotype could easily be demonstrated in archival hairs removed from the mother during early childhood. On the other hand, a

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particularly severe phenotype was seen in a pedigree in which some of the affected individuals exhibited an Hb6 Glu402Asp mutation in both alleles, thus indicating that the homozygous mutation acted in a codominant manner (Langbein and Schweizer, 2005).

This obviously coherent picture of the disease was, however, obscured by sporadic reports in which, despite a vertical transmission of the disease, no mutations could be found in one of the three type II cortex keratins (Richard *et al.*, 1996). Conceptually, this observation could seem plausible insofar as, besides mutated type II epithelial keratins, mutated type I epithelial keratins also are almost equally involved in the etiology of blistering genodermatoses. Surprisingly, however, despite the high number of type I hair keratins expressed in the cortex (Ha1, Ha3-I, Ha3-II, Ha4, Ha6, Ha8), up to now, mutations in the respective genes could not be demonstrated in affected members of those pedigrees that scored negative for type II cortex keratin mutations. Moreover, as several cases with clearly autosomal recessive transmission have been reported for monilethrix (Hanhart, 1955), one was left with the conclusion that further genes must be causally involved in the etiology of the condition.

It now appears that at least the riddle of the autosomal recessive player has been solved. Three independent papers in this issue provide convincing evidence that the culprit is the transmembranous adhesion molecule desmoglein 4, a member of the two desmosomal cadherin subfamilies, desmocollins (DSCs) and desmogleins (DSGs) (Shimomura *et al.*, 2006; Schaffer *et al.*, 2006; Zlotogorski *et al.*, 2006). Decidedly, this discovery took a particularly convoluted path. In 1996 and 2000, respectively, researchers from the Jackson Laboratory described two novel autosomal recessive mouse mutants, lanceolate hair (*lah*) and lanceolate hair-J (*lah*^{J}) (Montagutelli *et al.*, 1996; Sundberg *et al.*, 2000). Compared with the skin of wild-type mice, the skin of newborn mutant mice was slightly scaly, felt thicker and stiffer, and developed only a few short, fragile hairs, which disappeared within a few months, leading to lifelong alopecia. Occasionally, remaining hairs exhibited a variety of shaft abnormalities such as trichorrhexis nodosa and pili torti, but their hallmark was a marked enlargement of the distal end, which was similar to a lance head — hence the mutant name. Another characteristic feature within the lower follicle was premature differentiation and degeneration processes around the apex of the dermal papilla, leading to a prominent precortical swelling that was pushed up by the growing hair and thought to shape the characteristic lance-head tip (Montagutelli *et al.*, 1996; Sundberg *et al.*, 2000).

Initially, the two mouse mutants were thought to be related to the human ectodermal dysplasia Netherton's syndrome, but this view was abandoned, for in 2000 the causal gene for the syndrome, *SPINK5*, encoding the serine protease inhibitor LEKT1, was found to be located on chromosome 5q32 (Chavanas *et al.*, 2000), and both lanceolate mutants mapped to the centromeric end of mouse chromosome 18, which is syntenic to human chromosome 18q21 (Montagutelli *et al.*, 1996; Sundberg *et al.*, 2000). On the other hand, this region was known to harbor a cluster of genes involved in intercellular structures including adhesion molecules such as

Table 1. Desmoglein 4 mutation spectrum in localized autosomal recessive hypotrichosis (LAH) (a), autosomal recessive monilethrix (b), and lanceolate hair mice and rats (c)

a

Families	Parent 1	Parent 2	Mutation type	Mutation 1	Mutation 2	Reference
2	Pakistan	Pakistan	Homozygous	EX5_8del	—	Kljuic *et al.*, 2003
3	Pakistan (USA)	Pakistan (USA)	Homozygous	EX5_8del	—	Rafiq *et al.*, 2004
1	Pakistan (UK)	Pakistan (UK)	Homozygous	EX5_8del	—	Moss *et al.*, 2004
1	Iraq	Iraq	Homozygous	Ala129Ser	—	Messenger *et al.*, 2005

b

1	Iraq	Iran	Compound heterozygous	216+1G→T	Pro267Arg	Schaffer *et al.*, 2006
6	Iraq	Iraq	Homozygous	Pro267Arg	—	Zlotogorski *et al.*, 2006
2	Iraq	Morocco	Compound heterozygous	Pro267Arg	Arg289X	Zlotogorski *et al.*, 2006
2	Iraq	Iran	Compound heterozygous	Pro267Arg	216+1G→T	Zlotogorski *et al.*, 2006
1	Iraq	Iran	Compound heterozygous	763delT	216+1G→T	Zlotogorski *et al.*, 2006
1	Iraq	Iran	Compound heterozygous	Pro267Arg	763delT	Zlotogorski *et al.*, 2006
1	Japan	Japan	Compound heterozygous	2039insT	Ser192Pro	Shimomura *et al.*, 2006

c

Species	Designation	Mutation type	Mutation	Reference
Mouse	Lanceolate hair, *lah/lah*	Homozygous	746insT	Kljuic *et al.*, 2003
Mouse	Lanceolate hair-J, *lah*^{J}/*lah*^{J}	Homozygous	Tyr196Ser	Kljuic *et al.*, 2003
Rat	Lanceolate hair, *lah/lah*	Homozygous	Glu228Val	Jahoda *et al.*, 2004
Rat	Spontaneous hypersensitive rat	Homozygous	Gln306X	Meyer *et al.*, 2004
Rat	Iffa Credo rat, "hairless"	Homozygous	EX2_10del	Bazzi *et al.*, 2004

the desmosomal cadherins, desmocollins, and desmogleins. At that time, three major desmocollins, DSC1–DSC3, were known in humans and mice, and the desmoglein family comprised three members in humans, DSG1–DSG3, and five in mice, Dsg1α, Dsg1β, Dsg1γ, Dsg2, and Dsg3. Of these, only mutations in DSC1 and the murine ortholog of DSG3 were known to produce a hair phenotype. In 2003, however, a fourth mouse and human desmoglein member, DSG4, was discovered, which displayed a strong expression in the entire cortex of the hair follicle and the granular layer of the epidermis (McGrath and Wessagowit, 2005). Concomitantly, a novel autosomal recessive human hair disorder, localized autosomal recessive hypotrichosis (LAH; OMIM #607903), was presented. Although the typical lance-head-shaped distal ends of hairs of lanceolate mice and rats were not reported, the telltale swelling in the precortical region of hair follicles could occasionally be observed in LAH patients. More importantly, linkage analysis revealed that the disorder clearly mapped to chromosome 18q21.1 (Rafique *et al*., 2003). Indeed, the analysis of the *DSG4* gene in two large LAH pedigrees as well as the two lanceolate mouse strains demonstrated that both disorders were due to homozygous *DSG4* mutations (Kljuic *et al*., 2003) (Table 1a and c). Subsequently, mutations in both *DSG4* alleles were reported in five further LAH families as well as in three spontaneous lanceolate rat mutants (Table 1a and c) (Rafiq *et al*., 2004; Moss *et al*., 2004; Bazzi *et al*., 2004; Jahoda *et al*., 2004; Meyer *et al*., 2004; Messenger *et al*., 2005), thus establishing human LAH and its animal version as an apparently well-defined autosomal recessive hypotrichosis.

It is therefore amazing that after several years of LAH research, we now learn from three independent and coincident studies that the disease can also comprise moniliform hairs as a further symptom. Remarkably, in affected individuals of the respective pedigrees, the beaded hair phenotype has been so well visible that, based on the non-vertical transmission of the trait and the negative scoring for type II hair keratin mutations, initially all 14 families investigated were clinically assigned to the recessive form of monilethrix (Shimomura *et al*., 2006; Schaffer *et al*., 2006; Zlotogorski *et al*., 2006). What exactly then led the authors to make the link with LAH is not explicitly stated. Presumably, casual reports of undulations in hair shaft diameter particularly in the *lah*^{J} mouse and one of the lanceolate rat strains were the reason for the decision to screen the patients for DSG4-based LAH. If one concedes that in the previous LAH studies, weakly formed moniliform hair may have been present but overlooked, it appears that, just as in the classical keratin-based monilethrix, considerable variations in the expression of the moniliform hair type might also exist in LAH patients.

> The observed overlap between monilethrix and LAH seems plausible, and the truly surprising aspect of this discovery is that it has been made so late.

In retrospect, however, the observed overlap between monilethrix and LAH seems plausible, and the truly surprising aspect of this discovery is that it has been made so late. The type II hair keratins Hb1, 3, and 6 as well as DSG4 are co-expressed in the cortex of the hair follicle. In addition, they are all part of the intricate desmosome–keratin complexes through which cortex cells are interconnected. Thereby the extracellular domains of the transmembranous DSG4 are involved in cell–cell adhesion and the intracellular DSG4 portions are linked to the cytoplasmic keratin intermediate filaments via desmoplakins (McGrath and Wessagowit, 2005). It is therefore conceivable that mutations either in the cortex keratins, compromising the keratin–desmoplakin interaction, or in *DSG4*, abrogating cell–cell adhesion, in cortex cells, entail a similar disease phenotype. In line with this, LAH-causing mutations were invariably located in the five extracellular repeat domains typical for all members of the cadherin superfamily that are indispensable for the hetero- or homophilic cadherin–cadherin interactions between cells. The mutation spectrum ranged from null mutations through the complete loss of several extracellular repeats to the substitution of a number of amino acids that are highly conserved in cadherins in which they either serve as phosphorylation sites or are part of Ca^{2+}-binding domains in the extracellular repeats necessary for cell–cell adhesion. Predictions for a genotype–phenotype correlation of the moniliform trait in LAH are at present difficult to make, given that the pedigrees shown in Table 1a have not been analyzed accordingly and that affected individuals from 12 of 14 families investigated in the new studies all carry a Pro267Arg mutation and exhibit a similar degree of hair beading (Table 1b). The frequent occurrence of this mutation in the Jewish Iraqi community (Table 1b) as well as the high incidence of the Ex5_8del mutation in Pakistani individuals from different geographical regions (Table 1a) suggests that these alleles represent ancestral mutations that have been widely spread.

Does the discovery of DSG4-based monilethrix provide a clue for the regularly beaded hair phenotype typical of the disease? Conceptually, it is evident that a periodically oscillating event must be at the base of the alternating node–internode formation. In the bulb region of the normal hair follicle there is a gradual conversion of proliferative matrix cells into differentiated cortex cells, which is regulated by a variety of sequentially interconnected signaling cascades. In contrast, in both LAH and lanceolate follicles, a premature and hasty differentiation occurs at the level of the apex of the dermal papilla. It may therefore be speculated that slight oscillations in the regulatory signaling cascades remain silent as long as they occur within an extended proliferation–differentiation gradient, but become amplified and phenotypically visible upon the breakdown of the gradient and abrupt differentiation.

In summary, the three new studies (Shimomura *et al*., 2006; Schaffer *et al*., 2006; Zlotogorski *et al*., 2006) have provided solid data according to which the autosomal recessive form of monilethrix can be regarded as a

clinical entity that overlaps with LAH. What remains unexplored is the further autosomal dominant version of monilethrix that is not related to type II cortex keratins. As, however, we know the causal genes for classical and LAH-associated monilethrix as well as their exact expression site in the hair follicle, we at least know where we have to look for the remaining culprit.

CONFLICT OF INTEREST

The author states no conflict of interest.

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